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DEVELOPMENT AND CHARACTERIZATION OF SOLID LIPID NANOPARTICLES OF LINAGLIPTIN

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Keywords:

Linagliptin, Solvent emulsification, Phospholipids, Entrapment efficiency, *in-vitro* drug release

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ABSTRACT: The main objective of the present research work was to formulate and characterize the linagliptin-loaded solid lipid nanoparticles (SLNs). SLNs possess distinctive characteristics like small and spherical shapes with an average diameter between 1to 100 nm. Linagliptin is used for the treatment of type II diabetes and it is a dipeptidyl peptidase 4-inhibitor and its oral bioavailability is 30%. The application of biopharmaceutical principles to the physicochemical properties of drug substance are characterized with the goal of designing best drug delivery system. The current research work was to enhance the oral bioavailability of linagliptin using the different phospholipids like stearic acid, glyceryl monostearate, cholesterol along with the surfactants like tween 80, span 80, poloxamer1 88, and span 20 by solvent emulsification/solvent evaporation method and solvent emulsification method in order to obtain the best novelty formulation. The prepared formulations have been evaluated for particle size analysis, zeta potential, percentage drug entrapment efficiency, scanning electron microscopy studies, *in-vitro* drug release kinetics, and stability studies. FT-IR spectra showed the there was no incompatibility between linagliptin and excipients. Formulations containing glyceryl monostearate and surfactants like poloxamer188 showed smaller particle size, greater drug release, and higher percentage entrapment efficiency. The best formulation F10, exhibited 687.2 nm particle size and 99.25% drug release.

INTRODUCTION: The oral route of drug delivery is the most conventional and preferred one. But there are limitations due to a number of factors with respect to the drug and formulation. The major causes include hepatic first-pass metabolism that results in low oral bioavailability and high lipophilicity of the drug, hence hindering the use of oral route of drug delivery. Diabetes mellitus is a chronic and metabolic disorder that results from the lack of insulin secretion, a relative lack of insulin action, and characterized by high levels of blood sugar.

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The percent of diabetes occurrence is increasing enormously due to lifestyle and age [1, 2]. Presently, several research works are being conducted to find newer ways in the management of diabetes [3]. One of the best options is the utilization of nano-medicine in diabetes management, which is the most promising one. Globally, an estimated 422 million adults were living with diabetes in 2014, compared to 108 million in 1980.

The global prevalence (age-standardized) of diabetes has nearly doubled since 1980, rising from 4.7% to 8.5% in the adult population, depicting 8.3% of the world population, and the number is expected to surge to 592 million by the year 2035 [4, 5]. Solid lipid nanoparticles (SLNs) are the colloidal drug carrier systems that contain solid lipid particles dispersed in 10 to 1000 nm size range. SLNs were found to have applications in oral, intramuscular, intravenous, ophthalmic, dermal,

rectal, and other modes of administration [6]. SLNs have been declared to blend the advantages of various other colloidal systems like fat emulsions, polymeric nanoparticles, micelles, and liposomes while evading their limitations concurrently. Few of the anticipated advantages by means of solid lipid nanoparticles include increased oral bioavailability of poorly aqueous soluble drugs, improved stability of drugs, targeted drug release, controlled release of drugs, the greater payload of drugs, reduced toxicity, and negligible use of organic solvents as well as ease of scale-up for the large scale production [7].

Linagliptin is a dipeptidyl peptidase 4- inhibitor used in the treatment of type II diabetes. The major disadvantage of linagliptin is its low oral bioavailability (29.5%) because of its first-pass metabolism in the liver and intestine. In order to overcome the particular challenge, linagliptin was formulated as solid lipid nanoparticles [8]. The present research work was mainly focused on developing solid lipid nanoparticles containing linagliptin as the model drug. The rationale for the choosing of solid lipid nanoparticles as the formulation approach was the ability of solid lipid nanoparticles to impart all the attributes of nanoformulation as well as enhanced bio-compatibility in comparison with the polymeric nanoparticles. SLNs have also been proclaimed to exhibit a controlled drug release profile in addition to a reduced toxicity profile. Furthermore, the formulation of SLNs has been reported hitherto for linagliptin and established to be favorable in terms of oral bioavailability.

MATERIALS AND METHODS: Linagliptin was obtained as a gift sample from Hetero Drugs Pvt. Ltd., Hyderabad, India. Cholesterol was purchased from Loba chemie, Tarapur. Poloxomer 188 was obtained from Evonil Degussa GmBH. Glyceryl monostearate procured from Avanti Polar Liquids. Tween 20, span 20, and span 80 were purchased from Merck, Mumbai. Methanol, sodium chloride, disodium hydrogen phosphate, and potassium dihydrogen phosphate were purchased from Fisher Scientific.

Drug Carrier Excipients Compatibility Testing: The drug linagliptin and the excipients interaction studies were performed by checking physical appearance as well as using the FT-IR analytical method. The interaction studies were done in order to assess any type of interaction of drug linagliptin with that of excipients utilized in the development of solid lipid nanoparticles of linagliptin.

Fourier Transform Infra-Red (FT-IR) Analysis [9]: An FT-IR spectrophotometer was utilized for the infrared analysis of the samples. Around 4-5 mg of sample was properly mixed with dry potassium bromide, and then the sample was analyzed over wave numbers ranging from 4000 - 400 cm^{-1} at transmission mode.

Formulation Development:

Calibration of Standard Curve of Linagliptin:

Determination of Wavelength: Primary stock solution was prepared by dissolving 10 mg of linagliptin pure drug in 10 ml of ethanol. 1 ml was taken from the primary stock solution into a 10 ml volumetric flask, and then the volume was adjusted to 10 ml with phosphate buffer solution pH 7.4 (secondary stock: 100 µg/ml). 1 ml was taken from the secondary stock solution, and volume was made up to 10 ml with phosphate buffer solution pH 7.4 (working stock: 10 µg/ml). The final concentration solution prepared was scanned between 200 nm - 400 nm using UV–visible spectrophotometer on spectrum mode in order to determine λ_{max} of linagliptin.

Preparation of Standard Graph of Linagliptin in Phosphate Buffer Solution pH 7.4: Aliquots of secondary stock solution were taken, and volume made up to 10 ml with pH phosphate buffer solution 7.4 to obtain the concentrations of 1 µg/ml, 2 µg/ml, 3 µg/ml, 4 µg/ml and 5 µg/ml concentrations, respectively. The solutions prepared were subjected to UV–visible spectrophotometric analysis at the determined λ_{max} for linagliptin utilizing phosphate buffer solution, pH 7.4 as blank. The calibration curve was constructed by taking concentration on X-axis and absorbance on Y-axis. The regression equation and correlation coefficient were determined.

Preparation of Solid Lipid Nanoparticles of Linagliptin:

Solvent Emulsification / Evaporation Technique [10, 11]: Solid lipid nanoparticles of linagliptin were fabricated by solvent emulsification/evaporation

technique. Accurately, a weighted amount of linagliptin was dissolved in methanol. Lipids used, such as cholesterol, stearic acid, were first warmed to 75 ºC. Drug and excipient proportions were taken as depicted in **Table 1**. The surfactants were added to the water under constant stirring and allowed to equilibrate to 75 ºC. Aqueous surfactant solution was added to the molten lipid and once again allowed to equilibrate at 75 ºC. The organic solvent mixture was completely evaporated at 70 ºC using a rotary evaporator (ROTALAB, Lab India). Drug entrapped lipid layer was subsequently poured into 100 ml of aqueous solution containing surfactant at 70 ºC using a magnetic hot plate and homogenized for 10 min at homogenization speed of 25,000 rpm using a high-speed homogenizer (IKA). Then, the suspension was allowed to cool at room temperature. The obtained SLNs dispersion was freeze-dried using a freeze dryer (Ilshin® Lab Co. Ltd., India) for 24 h at −50 ºC temperature and pressure below 15 Pascal.

TABLE 1: FORMULATION OF SOLID LIPID NANOPARTICLES OF LINAGLIPTIN BY SOLVENT EMULSIFICATION / EVAPORATION TECHNIQUE

Formulation Code	Drug* (mg)	Cholesterol (g)	Tween 20 (ml)	Span 20 (ml)	Methanol (ml)	Distilled Water (ml)
F1	100	0.3	0.1	-	10	q.s
F2	100	0.3	-	0.1	10	q.s
F3	100	0.3	-	0.1	10	q.s
Formulation code	**Drug* (mg)**	**Stearic Acid (g)**	**Span 80 (ml)**	**Span 20 (ml)**	**Methanol (ml)**	**Distilled Water (ml)**
F4	100	0.3	-	0.1	10	q.s
F5	100	0.3	-	0.1	10	q.s
F6	100	0.3	0.1	-	10	q.s

Drug * - linagliptin loaded SLNs

B. Solvent Emulsification Method [12]: Six formulations of linagliptin-loaded solid lipid nanoparticles were made using different surfactants and lipids in different ratios shown in **Table 2**. The drug and lipid solution is dissolved in methanol and chloroform. The organic solvents mixture gets evaporated using a rotary evaporator at 70 °C. The organic solvent mixture gets evaporated & purging with nitrogen gas to remove traces of organic solvent. Drug entrapped lipid layer poured into 100 ml of an aqueous solution containing surfactants like poloxamer 188 at 70 °C using a hot plate and homogenized for 10 min at homogenization speed of 25,000 rpm using ultra turrax.

Suspension was cooled at ice bath for 10 min and SLNs dispersion then subjected to lyophilization for 24 h at -50 °C and pressure below 15 pascals.

TABLE 2: FORMULATION OF SOLID LIPID NANOPARTICLES OF LINAGLIPTIN BY SOLVENT EMULSIFICATION METHOD

Formulation Code	Drug* (mg)	Cholesterol (g)	Poloxamer 188 (ml)	Tween 20 (ml)	Methanol (ml)	Distilled Water (ml)
F7	100	0.2	0.1	-	10	q.s
F8	100	0.2	-	0.1	10	q.s
F9	100	0.2	0.1	-	10	q.s
Formulation Code	**Drug* (mg)**	**GMS (g)**	**Poloxamer 188 (ml)**	**Tween 20 (ml)**	**Methanol (ml)**	**Distilled Water (ml)**
F10	100	0.1	0.1	-	10	q.s
F 11	100	0.1	-	0.1	10	q.s
F12	100	0.1	0.1	-	10	q.s

Drug * - Linagliptin loaded SLNs, GMS – Glyceryl monostearate

Characterization of SLNs of Linagliptin:

Particle size and Zeta Potential [13, 14]: The particle size was measured by dynamic light scattering technique using Horiba scientific nanopartica instrument. Zeta potential was estimated on the basis of electrophoretic mobility under an electric field. The samples were diluted with distilled water before measurement and measured at a fixed angle of 165° at 25 ºC for the particle size analysis.

For zeta potential measurement, samples were diluted with distilled water.

Drug Entrapment Efficiency [15]: The entrapment efficiency of the drug was determined by measuring the concentration of free drugs in the dispersion medium. 10 mg of freeze-dried SLNs of linagliptin was dissolved in aliquot volumes of phosphate buffer pH 7.4 and then filtered utilizing 0.45 μm membrane filters.

Absorbance of the filtered solutions were recorded by UV-visible spectrophotometer at 228 nm (Lab India). The percentage entrapment efficiency (% EE) was calculated by using the following formula:

% EE = (Mass of the drug in submicron particles) / (Mass of drug used in Formulation) × 100

Shape and Surface Morphology [16, 17]: The shape and surface morphology of the optimized freeze-dried linagliptin-loaded SLNs formulation was studied by scanning electron microscopy (SEM).

***In-vitro* Drug Release Studies [18]:** *In-vitro* drug release studies were carried out using pH 7.4 phosphate buffer consisting of 0.5% v/v Tween 80 by the dialysis bag method utilizing the dialysis membrane.

SLNs dispersion equivalent to 5 mg of linagliptin drug was then filled into the dialysis membrane bag & tied at both ends, and kept in a beaker consisting 100 ml of phosphate buffer solution pH 7.4. The speed and temperature were maintained at 100 rpm and 37 ± 2 ºC, respectively, using magnetic stirrer.

The samples were withdrawn at predetermined time intervals, and similar volume was simultaneously replaced with the fresh buffer solution in order to maintain the sink conditions.

The samples were analyzed at 228 nm using a UV-visible spectrophotometer. Cumulative % release was further calculated from the amount of linagliptin drug release.

The drug release kinetics were determined for the best formulation by following kinetic equations like zero-order (cumulative % release *vs*. time), first-order (log % drug remaining *vs*. time).

Higuchi's model (cumulative % drug release *vs*. square root of time) and Korsmeyer-Peppas model (log drug release *vs.* log time).

The values of r^2 were calculated from the linear curve obtained by regression analysis of plots. For the Korsmeyer-Peppas model, the value of n was computed.

Stability Studies [19, 20]: The stability studies of the best SLNs formulation were performed by storage at 30 ºC ± 2 ºC / 65% ± 5% RH for 90 days and were examined at periodic time intervals for the changes in particle size and % entrapment efficiency.

RESULTS AND DISCUSSION:

Drug Excipients Compatibility Studies: The interaction studies were carried out to ascertain any kind of interaction of drug with the excipients used in the preparation of solid lipid nanoparticles.

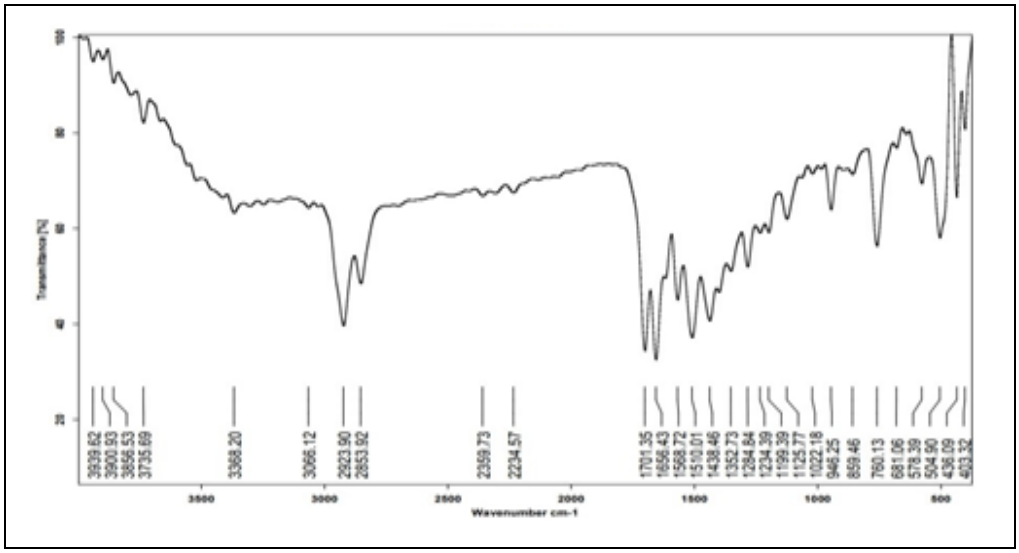

FIG. 1: FT-IR SPECTRA FOR LINAGLIPTIN

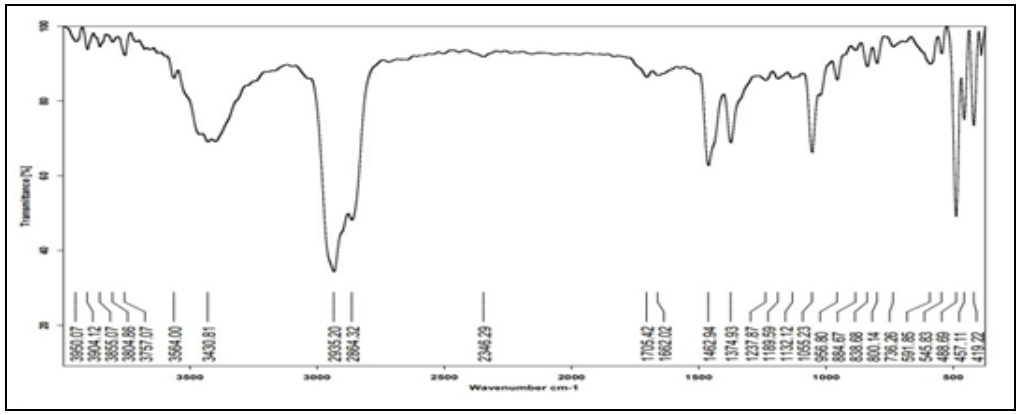

FIG. 2: FT-IR SPECTRA OF CHOLESTEROL

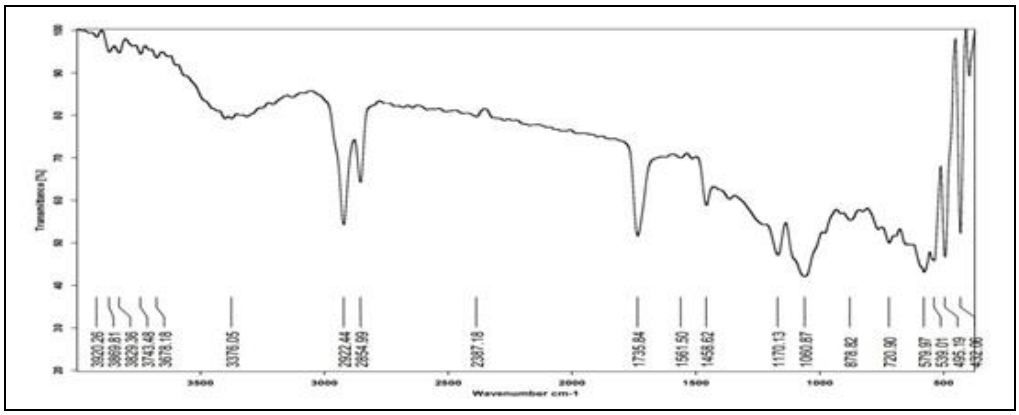

FIG. 3: FT-IR SPECTRA OF SPAN 20

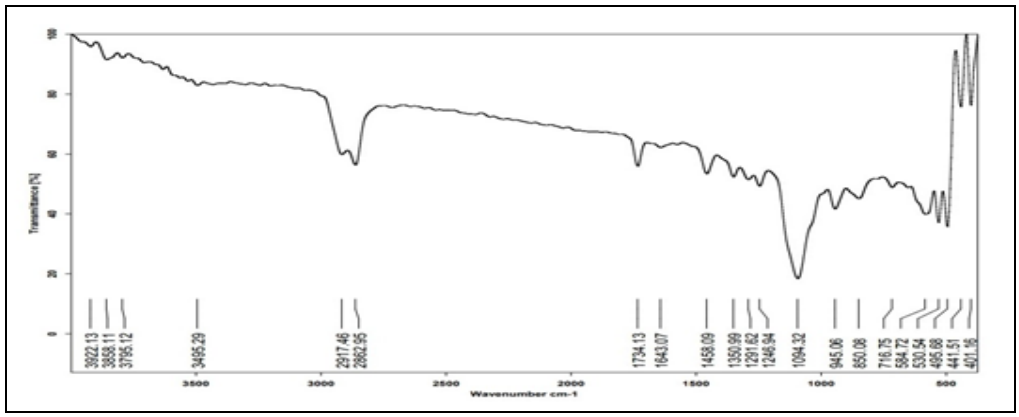

FIG. 4: FT-IR SPECTRA OF TWEEN 20

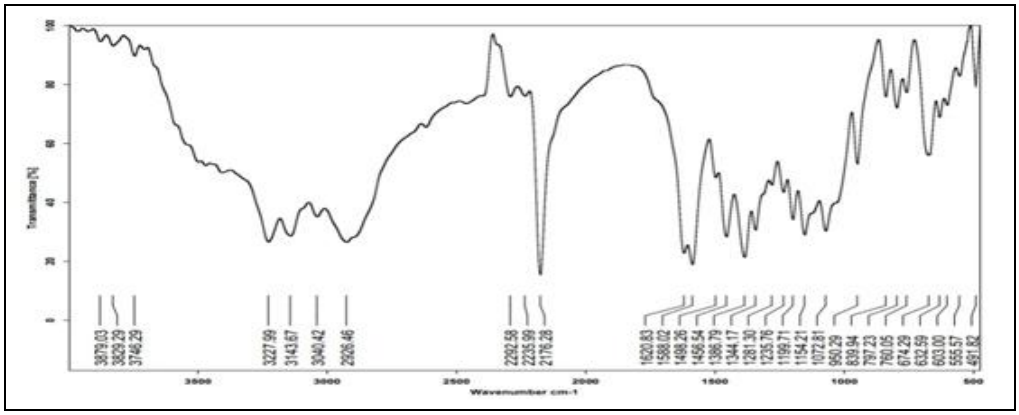

FIG. 5: FT-IR SPECTRA OF LINAGLIPTIN SLN FORMULATION (F10)

From the FT-IR spectra, it was revealed that there was no chemical interaction of the pure drug linagliptin with excipients used in the formulation of SLNs.

Inference: FT-IR studies were performed to check the possible interaction between chosen drug - linagliptin; and other ingredients used in the formulation of SLNs.

FT-IR of linagliptin pure drug showed the following peaks at 3735.69 cm^{-1}, 3368.20 cm^{-1}, 2923.0 cm^{-1}, 2234.57 cm^{-1}, 1701.35 cm^{-1}, 1656.43 and 1352.73 cm^{-1} due to O-H, N-H, C-H, C=O, C=C and O-H functional groups. From the FTIR spectra, it was revealed that there was no interaction between the selected drug and other excipients.

Formulation Development: Spectrophotometric determination and standard curve of linagliptin**.** Estimation of linagliptin was done using UV-visible spectrophotometric method in phosphate buffer solution, pH 7.4.

The standard concentration was scanned over a range of 400 nm – 200 nm which resulted in a peak at the wavelength of 228 nm, and it was considered as absorption λ_{max} for linagliptin.

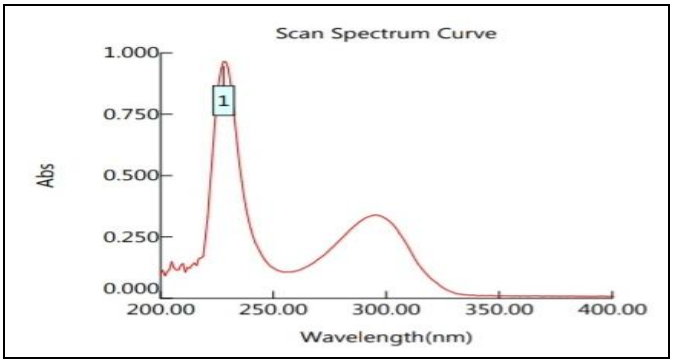

FIG. 6: SCAN SPECTRUM CURVE OF LINAGLIPTIN USING UV-VISIBLE SPECTROPHOTOMETER

The calibration curve of linagliptin in phosphate buffer solution pH 7.4 was constructed by making the solutions of 1 µg/ml, 2 µg/ml, 3 µg/ml, 4 µg/ml and 5 µg/ml. The absorbance of the solutions was measured by using UV-visible spectrophotometer at the λ_{max} of 228 nm.

The calibration graph was plotted by taking the concentrations on X-axis and absorbance on Y-axis.

Linagliptin concentration and absorbance followed a linear relationship, and the correlation coefficient (R^2) value in phosphate buffer solution pH 7.4 was observed to be 0.999, as depicted in **Table 3** & **Fig. 7.**

TABLE 3: STANDARD CALIBRATION CURVE OF LINAGLIPTIN

Concentration (µg/ml)	Absorbance at 228.0 nm (in Phosphate Buffer Solution, pH 7.4)
0	0
1	0.218
2	0.379
3	0.582
4	0.785
5	0.966

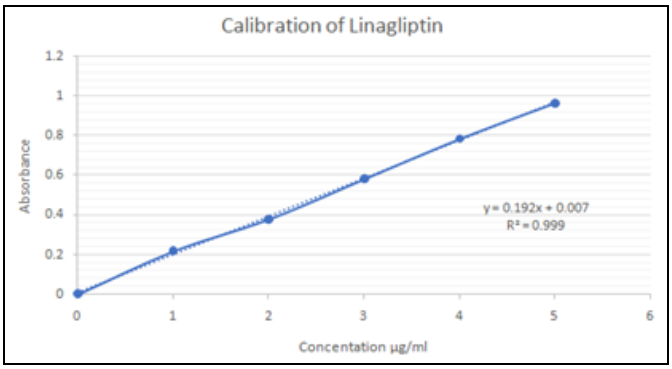

FIG. 7: STANDARD CALIBRATION CURVE OF LINAGLIPTIN IN PHOSPHATE BUFFER SOLUTION, pH 7.4

Preparation of Solid Lipid Nanoparticles of Linagliptin: A total of 06 solid lipid nanoparticles formulations of linagliptin were prepared by solvent emulsification/evaporation method and 06 linagliptin SLNs formulations by solvent evaporation technique using various lipids and surfactants.

Characterization of SLNs of Linagliptin:

Particle Size, Polydispersity Index (PDI) and Zeta Potential: The particle size of the developed linagliptin SLNs were measured before freeze-drying using a zeta sizer (Horiba Scientific). The particle size was found to be in the range of 385.9 to 1213.2 nm with zeta potential -12.7 to -20.1 mV for the prepared formulations of linagliptin SLNs. It was observed that SLNs formulations prepared by solvent emulsification/evaporation technique using stearic acid and span 80 showed decreased particle size compared to other formulations. The results of particle size, PDI, and zeta potential of various formulations were summarized in **Tables 4** & **5.**

TABLE 4: PARTICLE SIZE AND ZETA POTENTIAL OF LINAGLIPTIN SLN FORMULATIONS (F1 – F6)

Formulation Code	Particle Size (nm) ± SD	PDI	Zeta Potential (mv)
F1	827.4 ± 28.9	0.270	-20.1
F2	956.7 ± 45.2	0.294	-13.5
F3	1190.2 ± 24.2	0.325	-18.5
F4	1024.3 ± 33.9	0.318	-15.2
F5	856.0 ± 31.1	0.243	-16.8
F6	798.5 ± 55.0	0.210	-17.4

TABLE 5: PARTICLE SIZE AND ZETA POTENTIAL OF LINAGLIPTIN SLN FORMULATIONS (F7 – F12)

Formulation Code	Particle Size (nm) ± SD	PDI	Zeta Potential (mv)
F7	887.4 ± 36.51	0.271	-19.6
F8	1319.2 ± 32.63	0.394	-14.9
F9	753.6 ± 22.92	0.342	-13.2
F10	687.2 ± 20.18	0.253	-17.0
F11	703.9 ± 52.39	0.362	-18.3
F12	747.6± 36.65	0.269	-12.7

Drug Entrapment Efficiency: The percentage of drug entrapment was found to be variable in the range of 40.2% to 76.2%. The % EE was observed to be higher for SLNs formulations prepared with glyceryl monostearate and poloxomer 188 combinations *(i.e.,* SLNs formulations F10 to F12) as depicted in **Tables 6 & 7**. It has been observed that linagliptin-loaded SLNs formulation F10 showed higher % EE, *i.e.,* 76.2% in comparison with other formulations.

TABLE 6: % EE OF LINAGLIPTIN SLN FORMULATIONS (F1 – F6)

Formulation Code	% EE ± SD (n=3)
F1	40.2 ± 2.06
F2	47.6 ± 1.88
F3	45.7 ± 1.67
F4	56.5 ± 2.34
F5	59.1 ± 2.72
F6	62.4 ± 3.91

TABLE 7: % EE OF LINAGLIPTIN SLN FORMULATIONS (F7 – F12)

Formulation Code	% EE ± SD (n=3)
F7	68.8 ± 1.46
F8	62.2 ± 2.37
F9	66.3 ± 1.65
F10	76.2 ± 1.15
F11	73.9 ± 2.24
F12	74.6 ± 1.53

Shape and Surface Morphology: The shape and surface morphology of the best formulation F10 was studied by using scanning electron microscopy. The SEM micrograph revealed that the particles were found to be spherically shaped with a smooth surface, as shown in **Fig. 8.**

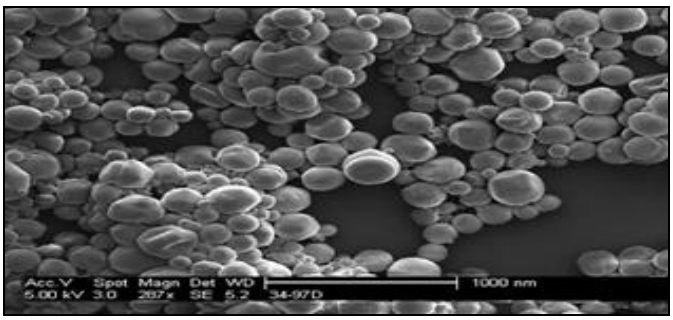

FIG. 8: SEM MIRCOGRAPH OF THE BEST LINAGLIPTIN SOLID LIPID NANOPARTICLE FORMULATION F10

***In-vitro* Drug Release Studies:** The *in-vitro* drug release studies were done for the duration of 12 h. The cumulative % drug release from F1 to F6 formulations was found to be 77.40%, 79.15%, 80.26%, 78.32%, 81.75% and 79.54%, respectively **Table 3** & **Fig. 13** and for F7 to F12 formulations was observed to be 97.56%, 96.64%, 95.59%, 99.25%, 98.37%, and 97.62%,, respectively.

TABLE 8: *IN-VITRO* RELEASE STUDIES OF LINAGLIPTIN SLN FORMULATIONS PREPARED BY SOLVENT EMULSIFICATION / SOLVENT EVAPORATION METHOD (F1 TO F6)

Time (min)	Cumulative % drug release					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
10	26.31± 0.34	24.26± 0.22	27.53± 0.60	28.20± 0.87	25.71± 0.37	24.75± 0.84
20	35.63± 0.42	39.37± 1.03	33.46± 1.24	38.45± 0.55	40.52± 0.84	32.60± 0.39
30	49.34± 0.28	55.69± 0.64	60.37± 1.08	44.26± 0.62	57.43± 0.37	43.69± 0.96
40	57.60± 0.35	64.30± 0.53	66.25± 0.82	55.30± 0.57	68.39± 0.82	57.40± 0.52
50	65.90± 1.12	70.22± 0.64	72.39± 1.38	69.32± 0.33	75.35± 0.90	67.22± 1.09
60	77.40± 0.89	79.15± 0.64	80.26± 1.05	78.32± 0.46	81.75± 0.62	79.54± 0.70

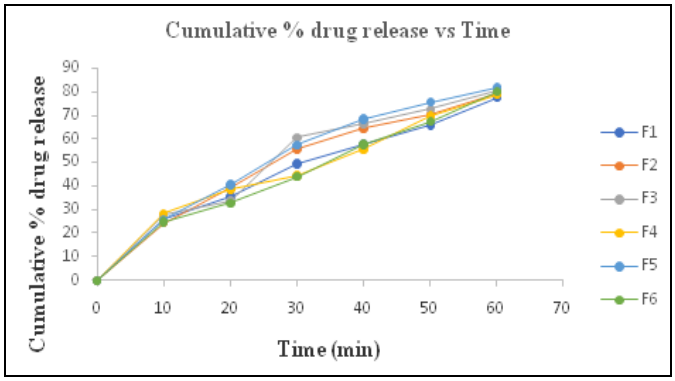

FIG. 9: DRUG RELEASE PROFILES OF LINAGLIPTIN SLNS FORMULATIONS (F1 TO F6)

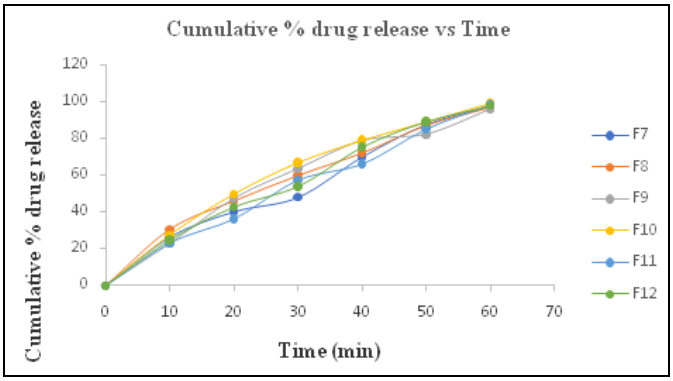

FIG. 10: DRUG RELEASE PROFILES OF LINAGLIPTIN SLN FORMULATIONS (F7 TO F12)

TABLE 9: *IN-VITRO* RELEASE STUDIES OF LINAGLIPTIN SLN FORMULATIONS PREPARED BY SOLVENT EMULSIFICATION TECHNIQUE (F7 TO F12)

Time (min)	Cumulative % Drug Release					
	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0
10	26.25 ± 0.28	30.54 ± 0.67	22.87 ± 0.45	27.65 ± 0.60	23.05 ± 1.19	24.75 ± 0.69
20	38.98 ± 0.46	45.86 ± 0.81	47.25 ± 0.67	49.85 ± 0.96	36.28 ± 0.85	42.63 ± 0.70
30	47.85 ± 1.10	59.69 ± 0.37	63.35 ± 0.54	66.89 ± 0.55	57.23 ± 0.63	53.89 ± 0.38
40	69.87 ± 0.85	71.96 ± 1.22	78.53 ± 0.38	79.03 ± 0.91	66.09 ± 0.80	75.25 ± 0.94
50	87.50 ± 1.13	86.92 ± 0.60	82.03 ± 1.05	89.05 ± 0.43	85.03 ± 0.37	89.05 ± 0.77
60	97.56 ± 0.72	96.64 ± 0.92	95.59 ± 0.88	99.25 ± 0.65	98.37 ± 0.72	97.62 ± 1.04

Kinetics of Drug Release: From results obtained, kinetics of linagliptin release from the best linagliptin SLNs formulation developed by solvent emulsification method is shown in **Table 10.**

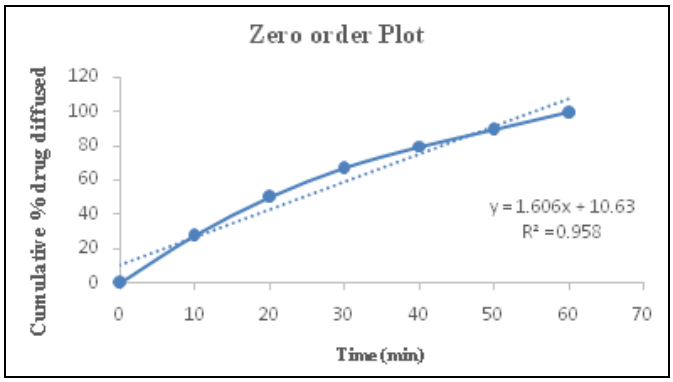

FIG. 11: DRUG RELEASE PROFILE FOR ZERO ORDER

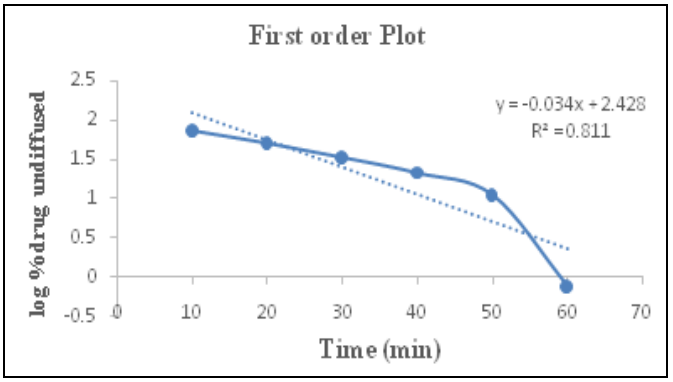

FIG. 12: DRUG RELEASE PROFILE FOR FIRST ORDER

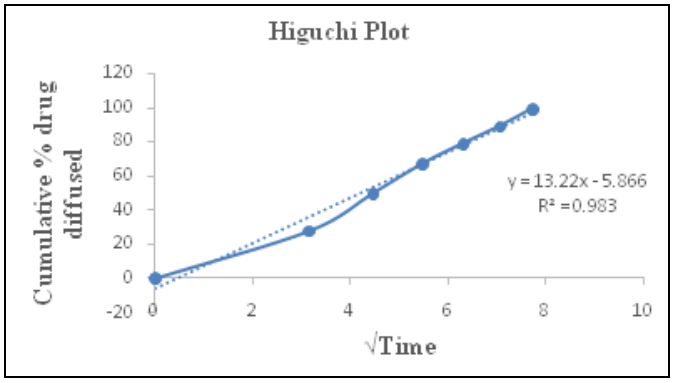

FIG. 13: DRUG RELEASE PROFILE FOR HIGUCHI MODEL

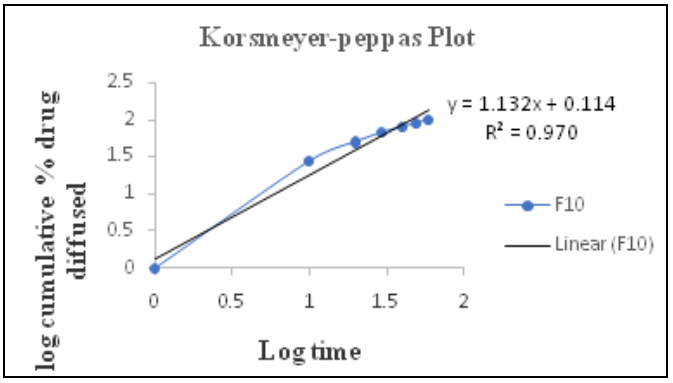

FIG. 14: DRUG RELEASE PROFILE FOR KORSMEYER-PEPPAS MODEL

TABLE 10: DRUG RELEASE KINETICS OF LINAGLIPTIN LOADED SLN F10

Zero order	First order	Higuchi	Korsmeyer-Peppas
0.958	0.811	0.983	0.970

Inference: For the best formulation F10, drug release kinetics study was carried out to evaluate the kinetics and mechanism of drug release. The kinetic data of formulation F10 could be best expressed by the zero-order equation as the plots showed linearity (R^2: 0.958) than first-order release kinetics (R^2: 0.811). From the release kinetics data, it was evident that the mechanism of linagliptin release from formulation F10 was non-fickian diffusion.

Stability Studies: The stability studies were carried out at 30 ºC ± 2 ºC / 65% ± 5% RH for 90 days and were examined at periodic time intervals for the changes in particle size and % entrapment efficiency.

The stability testing after 90 days led to the conclusion that there was negligible difference observed in the particle size and % entrapment efficiency of linagliptin SLN formulation stored for 90 days.

TABLE 11: STABILITY STUDIES FOR LINAGLIPTIN SLN FORMULATION (F10)

Storage Condition	Particle Size (nm) Mean ± SD			Entrapment Efficiency (%) Mean ± SD		
	Initial	30 days	90 days	Initial	30 days	90 days
30 °C ±2 °C / 65% ± 5% RH	687.2 ± 1.18	685.6±1.95	684.3±1.52	76.2±1.15	75.3±1.59	73.8±1.32

CONCLUSION: Linagliptin solid lipid nanoparticles were prepared by solvent emulsification / solvent evaporation and solvent emulsification method. It can be concluded that the developed solid lipid nanoparticles of linagliptin using glyceryl monostearate and poloxamer 188 shown a higher percentage of drug release and could enhance the oral bioavailability, which has to be further confirmed with *in vivo* studies. Solid lipid nanoparticles could be one of the alternative approaches to other colloidal drug delivery systems and tablets in order to enhance the bioavailability of the drugs.

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